REMARKS

Claims 44, 77 to 100, 102 and 104 to 113 were pending in the subject application. Applicants have herein amended claims 77 to 100, 102 and 104 to 113 to reflect the antecedent basis of the claims and have amended claims 82 and 89 to correct typographical errors. Applicants have also amended claims 44, 100 and 102. Support for the amendment to claim 44 may be found, *inter alia*, in the specification as originally filed on page 8, line 21, and page 15, lines 22 and 23. Support for the amendment to claim 100 may be found, *inter alia*, in the specification as originally filed on page 26, line 26, to page 27, line 1. Applicants have also added new claims 142 to 144 herein. Applicants note that the element "50-100 nucleotides in length" recited in claim 142 and the element "100-500 nucleotides in length" recited in claim 143 were previously presented in currently amended claim 102. Support for the amendment to claim 102 and for new claims 142 and 143 may be found, *inter alia*, in the specification as originally filed on page 15, lines 25 to 28. Support for new claim 144 may be found, *inter alia*, in the specification as originally filed on page 8, lines 21 to 24. After entry of this Amendment, claims 44, 77 to 100, 102, 104 to 113, 142 to 144 will be pending and under examination.

Third Party Submissions

Applicants note that the third-party submissions filed under 37 C.F.R. § 1.99 on 2/23/07 and 3/6/07 have been made of record in the subject application.

Claim Objection

The Examiner objected to claim 89 in view of its recitation of "a monocotyledonous plant of a dicotyledonous plant." The Examiner indicated that the word -or- should be substituted for "of".

In response, applicants have so amended claim 89.

Rejections Under 35 U.S.C. § 112, Second Paragraph (Definiteness)

The Examiner rejected claims 100 and 104 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, without conceding the accuracy of the Examiner's position and in order to expedite prosecution, applicants have amended claims 100 and 104 as suggested by the Examiner.

Rejections Under 35 U.S.C. § 102 - Haselbeck et al.

The Examiner rejected claims 44, 85-87, 90, 91, 93, 100, 102, 104-106, 110 and 111 under 35 U.S.C. § 102(b) as allegedly anticipated by Haselbeck et al. (Biochem. 32(33): 8575-8581,1993) (hereinafter "Haselbeck et al."). The Examiner alleged that Haselbeck taught Xenopus $tRNA^{Tyr}$ molecules comprising introns, and Xenopus oocytes comprising them. See abstract and Fig. 1 on page 8576. The Examiner alleged that the $tRNA^{Tyr}$ molecules comprise several sequences of at least 20 nucleotides that are identical to those in a $tRNA^{Tyr}$ transcript (i.e. a $tRNA^{Tyr}$). The Examiner alleged that the $tRNA^{Tyr}$ also contains several sequences that have partial complementarity to the first sequence, i.e. any sequence

that forms the 3' portion of a stem structure wherein the 5' portion of the stem structure consists of part of the recited first sequence of 20 nucleotides. The Examiner alleged that finally, the $tRNA^{Tyr}$ molecules comprise introns in the anticodon loop. See Figs. 1 and 3 on pages 8576 and 8577.

The Examiner indicated that claims 85 and 87 are included in the rejection because the status of the target gene as a transgene or an endogenous gene allegedly has no effect on the structure of the claimed isolated nucleic acid.

The Examiner indicated that claim 86 is included because tRNA genes are allegedly considered to be a multigene family.

The Examiner indicated that claim 100 is included because the entire sequence of $tRNA^{Tyr}$ is allegedly untranslated.

The Examiner alleged that regarding claim 102, the stuffer fragment can be considered to be the sequence of the 2 right-most introns in Fig. 1, or any portion of sequence between the first 20 nucleotides of the tRNA and the last 7 nucleotides of the tRNA.

In conclusion, the Examiner alleged that thus Haselbeck anticipates claims 44, 85-87, 90, 91, 93, 100, 102, 104-106, 110 and 111.

Applicants' Response

In response, without conceding the correctness of the Examiner's position and in order to expedite prosecution, applicants have amended claim 44 herein. Applicants note that that currently

amended claim 44 recites "[a]n isolated nucleic acid comprising: a first ribonucleotide (RNA) sequence of greater than 20 consecutive nucleotides which is identical in sequence to a region of a transcript of a target gene in a eukaryotic cell, a second RNA sequence of greater than 20 consecutive nucleotides which is identical to a complement of the greater than 20 consecutive nucleotides of said first RNA sequence, wherein the first and second RNA sequences of nucleotides are in the same nucleic acid and are separated and linked by a stuffer fragment which consists of a sequence of nucleotides" (emphasis added). Haselbeck et al. do not disclose an RNA sequence of greater than 20 consecutive nucleotides which is identical to a complement of another RNA sequence of greater than 20 consecutive nucleotides in the same nucleic acid.

Figure 1 of Haselbeck et al. (to which the Examiner refers) discloses a double-stranded, self-complementary structure. However, the double-stranded, self-complementary structure of Haselbeck et al. does not have "greater than 20 consecutive nucleotides" identical to a complement of another "greater than 20 consecutive nucleotides" in the same nucleic acid.

Therefore, Haselbeck et al. do not anticipate the clarified claim 44.

Applicants further maintain that Haselbeck et al. do not anticipate claims 77 to 84, 88, 89, 92, 94, 95 to 98, 100, 107 to 109, 110, 112 and 113, each of which depend from claim 44, and each of which recites additional independently novel and patentable features. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 44, 85-87, 90, 91, 93, 100, 102, 104-106, 110 and 111.

Rejections Under 35 U.S.C. § 103 - Agrawal et al., Kool and Buchman et al.

The Examiner rejected claims 44, 77, 80-87, 90, 91, 97-99, 102 and 104-113 under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal et al. (WO 94/01550, of record) in view of Kool (US 5,514,546) and Buchman et al. (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

The Examiner alleged that Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The Examiner alleged that the target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The Examiner alleged that the self complementary regions may be separated by an unpaired nucleotide loop structure (see e.g. Fig. 1, and page 15, lines 9-16). The Examiner alleged that the target gene may be a viral gene. The Examiner alleged that disclosed viruses include human immunodeficiency virus, Yellow Fever virus (a single strand (+) RNA virus), and Herpes simplex virus (a double stranded DNA virus). See paragraph bridging pages 10 and 11. The Examiner alleged that the target may be a member of a multi-gene family such as ras. See page 12, line 10. The Examiner alleged that the oligonucleotide may be in a pharmaceutically acceptable carrier. See claim 18. The Examiner alleged that absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to vary the length of the unpaired loop sequence of the self-stabilizing RNA of Agrawal in order to optimize hybridization of the complementary section of the oligonucleotides, thereby providing

increased stability against nucleolytic attack.

The Examiner asserted that Agrawal did not teach oligonucleotides comprising an intron.

The Examiner alleged that Kool taught delivery of stem-loop oligonucleotides by expression vector or by direct application of the oligonucleotides. See abstract; Fig. 1; column 3, lines 16-19 and lines 58-62; column 4, lines 6-17; and column 14, lines 39-. The Examiner alleged that Kool also disclosed antisense inhibition by targeting coding regions. See column 7, lines 43-46. The Examiner alleged that that Kool also disclosed delivery of expression vectors by viral- or liposome-mediated transfection. See column 15, lines 36-45; column 16, lines 43-47; paragraph bridging columns 24 and 25; and column 29, lines 32 and 33. The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the oligonucleotides of Agrawal by use of the expression vector of Kool. The Examiner alleged that M.P.E.P. § 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. The Examiner alleged that an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. The Examiner alleged that thus the delivery techniques of Kool, i.e. direct application of oligonucleotides, and transfection of oligonucleotide expression vectors, are considered to be exchangeable equivalents. The Examiner alleged that alternatively, the method of delivering the oligonucleotides can be viewed as a matter of design choice. The Examiner alleged that moreover, one would have been motivated to use the

expression vector of Kool in order to obtain continuous synthesis and action of oligonucleotides for the amount of time that the vector was present in the cell. The Examiner alleged that generally, expression vectors can be made with selectable markers that allow their maintenance in a cell for a longer time than the expected lifetime of an oligonucleotide. The Examiner alleged that thus one could reasonably expect to obtain antisense inhibition for a longer period of time with the expression vector of Kool.

The Examiner alleged that it would have been similarly obvious to target coding regions of target genes, and to deliver the vectors by viral or liposomal means as suggested by Kool.

The Examiner alleged that however, the combined references of Agrawal and Kool do not teach an RNA construct comprising an intron.

The Examiner alleged that Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed transcript by 400-fold. See abstract.

The Examiner alleged that it would have been obvious to include an intron in the expression vector of Kool in order to obtain the benefit of increased expression disclosed by Buchman. The Examiner alleged that the resulting transcripts would contain, prior to processing, an intron.

The Examiner alleged that thus the invention as a whole was prima facie obvious.

Applicants' Response

In response, applicants respectfully traverse.

Applicants respectfully submit that the claims as amended herein recite novel elements not taught by the combination of Agrawal et al. and the secondary references. Specifically, applicants maintain that 1) "a first RNA sequence of greater than 20 consecutive nucleotides which is identical in sequence to a region of a transcript of a target gene", 2) "a second RNA sequence of greater than 20 consecutive nucleotides which is identical to a complement of the greater than 20 consecutive nucleotides of said first RNA sequence" and 3) "separated and linked by a stuffer fragment" as recited in claim 44, are not disclosed by Agrawal et al.

With respect to the elements 1) and 2) of claim 44 listed above, Agrawal et al. do not disclose sense RNA sequences of greater than 20 consecutive nucleotides either as an individual element, or in combination with a second RNA sequence of greater than twenty consecutive nucleotides which is identical to a complement of the first. Applicants note that the Examiner has referred to Figure 1 of Agrawal et al. Figure 1 of Agarwal et al. discloses a representation of binding of twenty consecutive nucleotides of an oligonucleotide to a target. Besides not disclosing binding of "greater than 20 nucleotides", Figure 1 of Agarwal et al. is not a representation of a nucleic acid having any of the applicants' elements 1), 2) or 3).

Agrawal et al.'s only disclosure of length of the antisense "target hybridizing region" is that it "is from about 8 to about 50 nucleotides in length" (page 9, line 36 to page 10, line 1 of

Agrawal et al., referenced by the Examiner in the rejection). Applicants further note that while Agrawal et al. disclose that the "self-complementary region contains oligonucleotide sequences that are complementary to other oligonucleotide sequences within the oligonucleotide" (page 15, lines 3 to 6), Agrawal et al. do not disclose or suggest how much of the "self-complementary region" complements the "target hybridizing region" and how much does not. Applicants also note that Agrawal et al. disclose that "about 4 or more base-pairs will be necessary to maintain . . . the double-stranded structure" formed by the complementary binding of the "self-complementary region" and that the intramolecular base-pairing can involve every nucleotide. However, Agrawal et al. indicate that "about 10 intramolecular base-pairs" is "preferred" (page 15, lines 23 and 24).

Furthermore, there is no disclosure in Agrawal et al. of a nucleic acid that comprises an RNA sense sequence in combination with an RNA antisense sequence. Indeed, applicants maintain that the oligonucleotides of Agrawal are described as necessarily activating RNase H (see page 5, lines 9 to 12, and page 6, lines 1 and 2). To achieve this, applicants maintain that Agrawal et al.'s "target hybridizing region" must comprise a string of deoxyribonucleotides, rather than ribonucleotides. By this teaching, Agrawal et al. teaches away from an antisense sequence that is RNA as claimed by applicants.

Applicants also note that the Examples of Agrawal et al. do not provide any additional teaching that is relevant. Applicants note that the schematic molecule at the top of Figure 1 has only six intramolecular basepairs; the oligonucleotides of Figures 5 and 6 are entirely DNA and none shows more than 12 intramolecular basepairs; and the molecule of Figure 7 is a ribozyme and which

is also not relevant.

Yet furthermore, applicants respectfully submit that there is no suggestion to combine the disclosure of Agrawal et al. with those of Kool and Buchman et al. because the combination also fails to disclose each and every element of the pending claims. For example, one deficiency of Agrawal et al. with respect to applicants' claimed nucleic acid is that Agrawal et al. do not disclose the minimum length of a sense RNA sequence as claimed. This deficiency is not cured by the secondary art. Indeed, the cited secondary art would not motivate the skilled person to change the length of the "self-complementary region" let alone any portion of the self-complementary region that may correspond to a "sense sequence" so that it is greater than 20 nucleotides. Moreover, the cited secondary art would not motivate the skilled person to vary the oligonucleotides of Agrawal et al. so that they comprise antisense RNA sequences. Agrawal et al. teaches that the oligonucleotides activate RNase H and therefore necessarily comprise a stretch of DNA. Indeed, applicants maintain that there is no teaching in the cited secondary art that the molecules do not activate RNase H.

Finally, applicants respectfully submit that the combination of references is not practicable. Agrawal et al. discloses double-stranded or hairpin oligonucleotides that comprise at least some stretch of DNA. Applicants note that Kool discloses a stem-loop oligonucleotide and that Buchman et al. disclose the inclusion of an intron in a genetic construct. Applicants maintain that one of skill in the art was not able to predict whether the disclosure of Agrawal et al. could be combined with the disclosure of Kool and Buchman et al. to generate the claimed nucleic acids, and the August 7, 2007 Office Action offers no

explanation of the required predictability. Absent such predictability, the obviousness rejection cannot be proper. See, *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007).

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claims 44, 77, 80 to 87, 90, 91, 97 to 99, 102 and 104 to 113 under 35 U.S.C. § 103(a).

Rejections Under 35 U.S.C. § 103 – Agrawal et al., Day et al. and Buchman et al.

The Examiner rejected claims 44, 78, 79, 88, 89, 112 and 113 under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal et al. (WO 94/01550, of record) in view of Day et al. (Proc. Nat Acad. Sci. USA 88: 6721-6725, 1991), and Buchman et al. (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

In response, applicants respectfully traverse. Applicants maintain that Agrawal et al. does not disclose the claimed invention as discussed above. Applicants further maintain that the combination of Agrawal et al. with Day et al. and Buchman et al. is not practicable, and in any event does not disclose each and every element of the pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claims 44, 78, 79, 88, 89, 112 and 113 under 35 U.S.C. § 103(a).

Rejections Under 35 U.S.C. § 103 – Agrawal et al., Shewmaker et al. and Buchman et al.

The Examiner rejected claims 44, 88, 89, 99, 100, 112 and 113

under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal et al. (WO 94/01550, of record) in view of Shewmaker et al. (US Patent 5,107,065) and Buchman et al. (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

In response, applicants respectfully traverse. Applicants maintain that Agrawal et al. does not disclose the claimed invention as discussed above. Applicants further maintain that the combination of Agrawal et al. with Shewmaker et al. and Buchman et al. is not practicable, and in any event does not disclose each and every element of the pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claims 44, 88, 89, 99, 100, 112 and 113 under 35 U.S.C. § 103(a).

Rejections Under 35 U.S.C. § 103 - Agrawal et al., McGarry et al. and Buchman et al.

The Examiner rejected claims 44, 90, 92 and 94 under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal et al. (WO 94/01550, of record) in view of McGarry et al. (Proc Nat. Acad. Sci. USA 83:399-403,1986) and Buchman et al. (Mol. Cell. Biol. 8(10): 4395-4405, 1988).

In response, applicants respectfully traverse. Applicants maintain that Agrawal et al. does not disclose the claimed invention as discussed above. Applicants further maintain that the combination of Agrawal et al. with McGarry et al. and Buchman et al. is not practicable, and in any event does not disclose each and every element of the pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claims 44, 90, 92 and 94 under 35 U.S.C. § 103(a).

Rejections Under 35 U.S.C. § 103 - Agrawal et al., Kool, Buchman et al. and Barabino et al.

The Examiner rejected claims 93 and 95 under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal, Kool, and Buchman as applied to claims 44, 77, 80-87, 90, 91, 97-99, 102,104-113 above, and further in view of Barabino et al. (Mech. Dev. 63:133-143, 1997).

In response, applicants respectfully traverse. Applicants maintain that Agrawal et al. does not disclose the claimed invention as discussed above. Applicants further maintain that the combination of Agrawal et al. with Kool, Buchman et al. and Barabino et al. is not practicable, and in any event does not disclose each and every element of the pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claims 93 and 95 under 35 U.S.C. § 103(a).

Rejection Under 35 U.S.C. § 103 - Agrawal et al., Kool, Buchman et al. and Swamynathan et al.

The Examiner rejected claim 96 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal, Kool, and Buchman as applied to claims 44, 77, 80-87, 90, 91, 97-99, 102 and 104-113 above, and further in view of Swamynathan et al. (J. Virol. 71(4): 2873-2880, 1997).

In response, applicants respectfully traverse. Applicants maintain that Agrawal et al. does not disclose the claimed invention as discussed above. Applicants further maintain that there is no suggestion to combine the disclosure of Agrawal et al. with those of Kool, Buchman et al. and Swamynathan et al. because the combination does not disclose each and every element of the pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider the rejection of claim 96 under 35 U.S.C. § 103(a).

Rejections Under 35 U.S.C. § 103 - Fire et al. and any one of Szyf et al., Zamecnik or Urdea

The Examiner rejected claims 44, 77, 80-82, 85-95, 97-99 and 104-113 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire (US 6,506,559) in view of any one of Szyf et al (US Patent 5,578,716), Zamecnik (WO 97/11170), or Urdea (US Patent 5,631,148).

The Examiner alleged that Fire disclosed and claimed methods for regulating gene expression in cells, including plant and animal cells, comprising introducing into a cell a double stranded RNA comprising a sequence complementary to a portion of the target gene and a sequence identical to a portion of the target gene. The Examiner alleged that at column 4, lines 41-46 Fire et al. teach that the dsRNA can be formed from 1 or 2 strands. The Examiner alleged that at columns 7-9, Fire et al. teach that the RNA can be synthesized in vivo or in vitro, can be expressed from a vector and can have a length of greater than 25 nucleotides (see col. 7, lines 53-col.8, lines 12). The Examiner alleged

that the target gene can be a transgene (column 6, lines 44-49), a multigene family member (column 1, lines 13-16), a dicot (bean) or monocot (corn) plant gene (column 8, lines 14, 15, 20 and 21), a vertebrate, invertebrate, fish, mammal, human, or insect gene (column 8, lines 35-51).

The Examiner alleged that Fire also exemplifies a double stranded RNA comprising an intron. See Table 1 at column 23/24, "unc22C", and column 23 at line 60, which the Examiner alleged disclose that unc22C is a dsRNA comprising a 43 nucleotide intron that was injected into C. elegans.

The Examiner alleged that thus Fire taught single strand RNAs comprising a first sequence of greater than 20 nucleotides identical to a target sequence in the transcript of a target gene of a eukaryotic cell, a second sequence complementary to the first, and an intron.

The Examiner asserted that Fire was silent in regard to a stuffer fragment consisting of a sequence of nucleotides.

The Examiner alleged that Fire taught that double stranded RNA may be formed from a single self-complementary nucleic acid (forming hairpin dsDNA).

The Examiner alleged that Szyf taught that the hairpin structures disclosed therein "will presumably have loops of 4 or more nucleotides resulting from non-base-paired nucleotides" (US patent 5,578,716, col. 7, lines 29-33).

The Examiner alleged that similarly, Zamecnik taught that the sense and antisense regions of the disclosed duplexes may be

joined by a loop of 3-6 bases (see p. 8, lines 4-5).

The Examiner alleged that Urdea taught that a sequence of 1-100 nucleotides may intervene between the substrate binding region and the competitive binding sequence of the disclosed ribozyme oligonucleotides (see col. 7, lines 10-28).

The Examiner alleged that accordingly, it would have been obvious at the time the instant invention was made to modify the Fire patent to utilize a stuffer nucleotide fragment between the sense and antisense coding regions in a self-complementary nucleic acid in order to facilitate duplex formation as taught by the Szyf et al., Zamecnik or Urdea. The Examiner alleged that it would have been similarly obvious to target a region of any target gene wherein the region encompasses an intron, because Fire exemplified such.

Applicants' Response

In response applicants respectfully traverse.

Initially, applicants point out that U.S. Patent No. 6,506,559 to Fire et al. is not a valid prior art reference to the subject application. Applicants note that the first effective filing date of the subject application is March 20, 1998. Fire et al. issued from an application filed December 18, 1998, i.e. after the first effective filing date of the subject application.

Fire et al. do claim the benefit of U.S. Provisional Application No. 60/068,562, filed December 23, 1997 (the "Fire et al. Provisional"). Fire et al. Provisional, however, discloses less than U.S. Patent No. 6,506,559. Accordingly any rejection under

35 U.S.C. § 103 can at most be based on the disclosure of Fire et al. Provisional, not on the disclosure of U.S. Patent No. 6,506,559. The Fire et al. Provisional does not disclose at least each of the following elements of applicants' amended claims: 1) "a second RNA sequence of greater than 20 consecutive nucleotides which is identical to a complement of the greater than 20 consecutive nucleotides of said first RNA sequence", 2) "first and second RNA sequences of nucleotides are in the same nucleic acid" and 3) "separated by a stuffer fragment." The secondary references do not remedy these deficiencies of the Fire et al. Provisional.

With respect to the element 1) listed above, Fire et al. Provisional on page 6, lines 18 to 20 discloses a "double-stranded structure may be formed by a single self-complementary RNA strand . . .." However, a "double-stranded structure . . . formed by a single self-complementary RNA strand" includes, as the Examiner is aware, numerous possible nucleic acids, such as the molecule disclosed in Figure 1 of Haselbeck et al. for example. Applicants have hereinabove explained that the currently pending claims distinguish over Haselbeck et al. Applicants' claims also distinguish over a number of other possible "double-stranded structure[s]."

Element 1), as claimed herein, is not disclosed in the Fire et al. Provisional. More importantly, applicants' element 1) is neither at once envisaged, or obvious, from the phrase "double-stranded structure may be formed by a single self-complementary RNA strand . . ." in the Fire et al. Provisional. Applicants' element 1) is but one possibility from within a large number of possible species encompassed by the phrase in the Fire et al. Provisional. See, e.g. M.P.E.P. §§ 2131.02 and 2144.08.

With respect to element 2) there is no disclosure in the Fire et al. Provisional of a nucleic acid having both a first RNA sequence of greater than 20 nucleotides and a second RNA sequence of greater than 20 nucleotides. The mere disclosure of a "double-stranded structure" in the Fire et al. Provisional does not teach the length of even one RNA sequence, much less the length of both in one nucleic acid. Furthermore, applicants' element 2 is not at once envisaged, or obvious, from the Fire et al. Provisional. See, e.g. M.P.E.P. §§ 2131.02 and 2144.08.

With respect to element 3), the Fire et al. Provisional does not disclose a "stuffer" according to applicants' claims at least because the Fire et al. Provisional does not disclose the RNA sequences which are linked by the stuffer. More precisely, without defining applicants' element 1), it is not possible to envisage the stuffer that links the defined RNA sequences. Any element that cannot be envisaged from the prior art cannot be anticipated and cannot be obvious from the prior art. See, e.g. M.P.E.P. §§ 2131.02 and 2144.08.

None of the secondary references cited remedy these deficiencies of the Fire et al. Provisional discussed above.

Accordingly, applicants maintain that none of the pending claims are anticipated under 35 U.S.C. § 102 by the Fire et al. Provisional. Applicants further maintain that neither Szyf et al., Zamecnik nor Urdea overcome the deficiencies of Fire et al. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 44, 77, 80-82, 85-95, 97-99 and 104-113 under 35 U.S.C. § 103(a).

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $1,050.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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